IN RESPONSE TO YOUR QUESTIONS

ONCE DAILY
VIOXX®
(rofecoxib)

CARDIOVASCULAR SYSTEM

CLINICAL PROFILE IN OSTEOARTHRITIS STUDIES

VIOXX® (rofecoxib)

IN OA STUDIES

BASELINE CARDIOVASCULAR (CV) CHARACTERISTICS[1]

CV Risk Factors	Percentage of Patients at Baseline*
Hypertension	**39%**
Hypercholesterolemia	**11%**
Current smoker	**14%**
Diabetes	**7%**
History of angina/coronary artery disease (CAD)	**5%**
History of myocardial infarction (MI)	**3%**
Congestive heart failure (CHF)	**1%**

*Mean age: 63 years (range: 39–93). Gender: 70% female, 30% male.

VIOXX is indicated for:

- Relief of the signs and symptoms of osteoarthritis (OA).
- The management of acute pain in adults (see CLINICAL STUDIES).
- Treatment of primary dysmenorrhea.

Selected safety information

- VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.
- VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Common adverse events included upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).
- Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.
- With NSAIDs, most spontaneous reports of fatal gastrointestinal (GI) events are in elderly or debilitated patients
  —therefore, special care should be taken in treating these patients.

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CARDIOVASCULAR EVENT PROFILE

Cardiovascular thromboembolic adverse events in OA clinical trials†,1

- The overall incidence of cardiovascular thromboembolic adverse events was assessed. This review included events pertaining to cardiac (i.e., MI, angina), central nervous (i.e., CVA, TIA), and peripheral vascular (i.e., arterial embolism) systems.
- Due to the variable duration of treatment in the studies, results are expressed as events per 100 patient-years.

Cardiovascular Thromboembolic Adverse Events per 100 Patient-Years

	Placebo N=783	VIOXX 12.5 mg N=1,215	VIOXX 25 mg N=1,614	VIOXX* 50 mg N=526	Ibuprofen 2400 mg N=847	Diclofenac 150 mg N=590	Nabumetone 1500 mg N=128
Events**	2.9	3.2	2.6	3.3	2.6	3.1	3.9

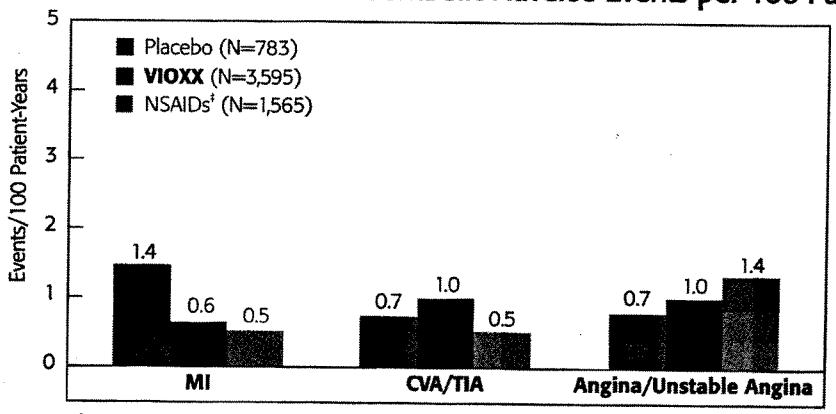
** MI, cerebrovascular accident (CVA), transient ischemic attack (TIA), and angina.

The incidence of events was similar among the groups.

***Recommended dosing in OA:** The recommended dose of VIOXX is 12.5 mg once daily. Some patients may receive benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Specific cardiovascular thromboembolic events†,1

Cardiovascular Thromboembolic Adverse Events per 100 Patient-Years



†Data are based on nine double-blind studies in approximately 6,000 OA patients actively taking VIOXX, active comparator, or placebo. Studies lasted from 6 weeks to a maximum duration of 86 weeks. The average duration of treatment was 5.5 months.

‡NSAIDs are from OA clinical studies and include diclofenac 150 mg, ibuprofen 2400 mg, and nabumetone 1500 mg.

The incidence of events was similar among the groups.

Selected safety information

- As with all NSAIDs, VIOXX should be used with caution in patients with fluid retention, hypertension, or heart failure.
- Serious GI toxicity can occur with or without warning symptoms with NSAIDs.

OA CLINICAL TRIALS

OVERALL MORTALITY RATES

Overall mortality and cardiovascular mortality*,[1]

Events per 100 Patient-Years

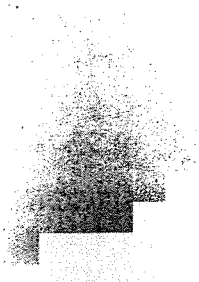
	VIOXX N=3,595	NSAIDs† N=1,565	Placebo N=783
Total mortality	0.1	1.1	0.0
Cardiovascular mortality	0.1	0.8	0.0

*Data are based on nine double-blind studies in approximately 6,000 OA patients actively taking VIOXX, active comparator, or placebo. Studies lasted from 6 weeks to a maximum duration of 86 weeks. The average duration of treatment was 5.5 months.

†NSAIDs are from OA clinical studies and include diclofenac 150 mg, ibuprofen 2400 mg, and nabumetone 1500 mg.

Selected safety information

- VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.
- Concomitant administration of low-dose aspirin with VIOXX may result in an increased risk of GI ulceration or other complications compared with use of VIOXX alone.
- Drug-interaction studies with VIOXX have identified potentially significant interactions with warfarin. Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing therapy with VIOXX in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In postmarketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.



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TOLERABILITY PROFILE

Clinical adverse events in OA studies

Occurring in ≥2% of Patients Treated With VIOXX and >Placebo, Regardless of Causality

Adverse Event	Once-Daily VIOXX 12.5 mg or 25 mg (N=2,829) %	Placebo (N=783) %	Ibuprofen 2400 mg daily (N=847) %	Diclofenac 150 mg daily (N=498) %
Fatigue	2.2	1.0	2.0	2.6
Dizziness	3.0	2.2	2.7	3.4
Lower extremity edema	3.7	1.1	3.8	3.4
Upper respiratory infection	8.5	7.8	5.8	8.2
Hypertension	3.5	1.3	3.0	1.6
Dyspepsia	3.5	2.7	4.7	4.0
Epigastric discomfort	3.8	2.8	9.2	5.4
Heartburn	4.2	3.6	5.2	4.6
Nausea	5.2	2.9	7.1	7.4
Sinusitis	2.7	2.0	1.8	2.4
Back pain	2.5	1.9	1.4	2.8
Bronchitis	2.0	0.8	1.4	3.2
Urinary tract infection	2.8	2.7	2.5	3.6

*Data are based on nine six-week to six-month clinical studies in OA patients taking VIOXX, active comparator, or placebo.

- In analgesia studies, the adverse-event profile of VIOXX 50 mg q.d. was generally similar to the adverse-event profile reported in the OA studies.
- In six-month OA studies using twice the maximum recommended dose, the general safety profile of VIOXX 50 mg q.d. was similar to that of VIOXX at recommended OA doses, except for a higher incidence of GI symptoms, lower extremity edema (6.3%), and hypertension (8.2%).
- The recommended doses for VIOXX in OA are 12.5 mg q.d. or 25 mg q.d.
- NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

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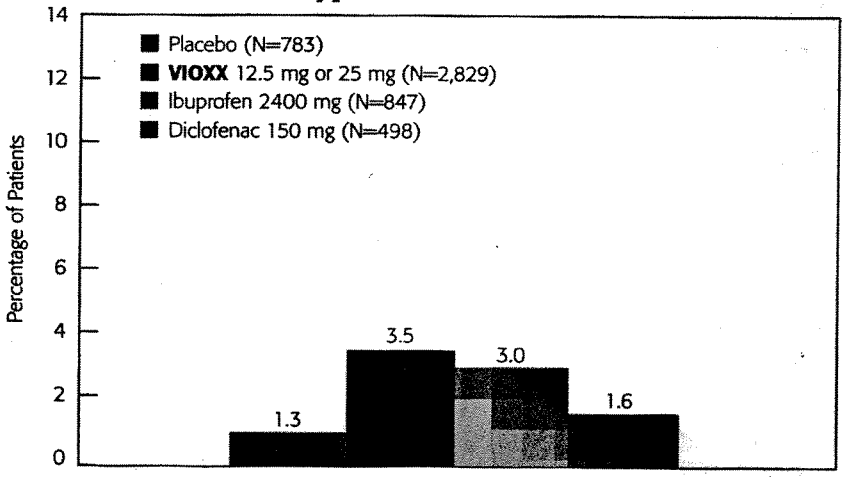
ADVERSE EVENTS PROFILE

Discontinuation rates for patients due to adverse events*,2

- Overall discontinuation rates due to any adverse event were low (6.7% for VIOXX 12.5 mg or 25 mg q.d. vs 4.2% for placebo).
- Low discontinuation rates for patients on VIOXX (12.5 mg or 25 mg q.d.) due to hypertension:
  — <0.1% of patients discontinued therapy due to hypertension

Incidence of hypertension*



*Data are based on nine double-blind six-week to six-month studies in approximately 6,000 OA patients taking VIOXX, active comparator, or placebo.

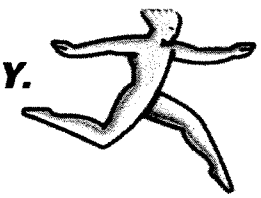
Selected safety information

- VIOXX is not recommended in patients with advanced kidney disease; no dosage adjustment is recommended in patients with mild to moderate kidney disease.
- Renal effects of VIOXX (e.g., hypertension, edema) were similar to those of comparator NSAIDs.
- Administration of NSAIDs has resulted in renal papillary necrosis and other renal injury, including acute renal failure.

Before prescribing VIOXX, please read the complete Prescribing Information.

References: 1. Daniels B, Seidenberg B. Cardiovascular safety profile of rofecoxib in controlled clinical trials. Paper presented at: 1999 Annual Scientific Meetings; November 13–17: Boston, MA. *Arthritis Rheum.* 1999;42(9 suppl):S143. Abstract 435. **2.** Data available on request from Professional Services, WP1-27, Merck & Co., Inc., West Point, PA 19486. Please specify information package DA-VIO14(1).

STRENGTH. SAFETY. QD SIMPLICITY.



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